

# PATENT

Rubin, *et al.*

Examiner: **Skibinsky, A. L.**

Group Art Unit: **1631**

Confirmation No.: **6145**

**APPELLANTS' REPLY BRIEF**

Dear Sir:

This Supplemental Reply Brief is submitted pursuant to 37 C.F.R. 41.43 (b) and 41.41, within two months from the mailing of the Supplemental Examiner's Answer which was mailed September 14, 2009, in response to the Appellants' Reply Brief submitted May 18, 2009, in response to the March 19, 2009 mailing of the Examiner's Answer which included a new ground of rejection. Applicants are filing this Supplemental Reply Brief in order to respond to the Supplemental Examiner's Answer which has withdrawn the previous newly added ground of rejection, but has maintained the original grounds of rejection.

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### ***I. Status of Claims***

Claims 40-48 are pending in this application. Claims 40-48 are being appealed. Of these claims, claim 40 is independent.

Claims 40-48 were finally rejected in the Final Office Action mailed June 10, 2008. A Notice of Appeal was filed via EFS on November 10, 2008. The Appeal Brief was filed via EFS on December 4, 2008, within two months of the filing of the Notice of Appeal. An Examiner's Answer was mailed March 19, 2009 and contained a New Ground of Rejection of claims 40-48. Appellants' Reply Brief was filed via EFS May 18, 2009 within two months of the mailing of the Examiner's Answer. A Supplemental Examiner's Answer was mailed September 14, 2009 withdrawing the previous newly added Ground of Rejection but maintaining the original Grounds of Rejection. This Supplemental Reply Brief is being filed in response to, and within two months of the mailing of, the Supplemental Examiner's Answer.

### ***II. Grounds of Rejection to be Reviewed on Appeal***

1. Whether claims 40-42 and 44-48 are unpatentable under 35 U.S.C. § 103(a) over Marks et al, in view of Kallal et al in further view of Proffitt et al.
2. Whether claim 43 is unpatentable under 35 U.S.C. § 103(a) over Marks et al, in view of Kallal et al in further view of Proffitt et al as applied to claims 40-42 and further in view of Dunlay, et al.

### ***III. Argument***

There are two pending rejections, the previous newly issued rejection under 35 U.S.C. § 101 was been withdrawn. The original two rejections of claims 40-48 remain. Claims 40-42 and 44-48 are rejected under 35 U.S.C. § 103(a) as obvious over Marks et al, in view of Kallal et al in further view of Proffitt et al. Claim 43 is rejected under 35 U.S.C. § 103(a) as obvious over Marks et al, in view of Kallal et al in further view of Proffitt et al as applied to claims 40-42 and further in view of Dunlay, et al.

#### **A. The Office Erred in Rejecting Claims 40-42 and 44-48 under 35**

**U.S.C. § 103(a) as being obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al.**

Claims 40-42 and 44-48 stand rejected as obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al. For the reasons set forth in the Appeal Brief filed December 4, 2008 and the Reply Brief filed May 18, 2009 and for the following reasons, the Appellants respectfully traverse.

**i. The cited references alone or in combination do not teach or disclose all of the claim limitations**

In order to establish a *prima facie* case of obviousness the Patent office must establish that the prior art references alone or in combination must teach or suggest *all* the claim limitations. MPEP § 706.02(j).

With respect to the cited art and the corresponding rejections laid out by the Examiner, Appellants reiterate their arguments which are fully outlined and discussed in the Appeal Brief filed December 4, 2008 and the Reply Brief filed May 18, 2009. However, for the sake of brevity in this Supplemental Reply Brief, Appellants will simply address the Examiner's response to the Appellants' arguments which begins on page 10 of the instant Supplemental Examiner's Answer.

Briefly, as admitted by the Patent Office in the rejection mailed June 10, 2008, "Marks in view of Kallal et al. does **not** teach calculating a number and or percent of the individual cells that internalized the at least first luminescently labeled reporter molecule." The Patent Office then asserts that Proffitt et al. cure this deficiency by teaching "a computerized scanning system and algorithm that is able to measure the relative cell numbers that contain a florescent label." The Patent Office further states that in Proffitt et al, "[t]he total relative fluorescence intensity for the entire well containing cell is determined..." While Proffitt is asserted to cure the deficiencies of Marks et al in view of Kallal et al. the Patent Office does not assert that Proffitt et al teach "calculating a number and or percent of the **individual cells that internalized the labeled reporter molecule**," but instead the Patent Office admits that Proffitt et al teach calculating the intensity of the "entire well" and measures "the relative cell number." Appellants' have previously argued in both the Appeal Brief and Reply Brief that Proffitt does not teach, suggest, or make obvious "calculating a number and or percent of the **individual cells that internalized the labeled reporter molecule** wherein the **calculations provide a**

**measure of internalization of the cell surface receptor protein in the individual cells.”** The Examiner responds to this argument in the instant Supplemental Examiner’s Answer by stating (page 11, ¶3) that

The instant claim reads on calculating the number of the plurality of cells as taught by Proffitt et al. The instant claim does not require calculating the number and/or percent of cells based on a determination of **each** individual fluorescing cell in the assay. It would be obvious for one of skill in the art to determine the number of individual cells since the plurality of cells in the wells comprise individual cells. Using the Fluorescence vs. Cells per well data of Figures 3-5. Proffitt et al. teach calculating 1000 cells/well using the data in Figure 5 (page 208, col. 1, two lines from bottom) to determine "excellent linearity in 6, 24, and 48 well plates," as given by the DIM-SCAN. Furthermore, though the instant study by Proffitt et al. is a test of the DIM-SCAN apparatus, Proffitt et al. teach that ultimately DIMSCAN is used to "quantify total or viable cell numbers in tissue culture plates" (page 205, col. 1, ¶1). Therefore, the art of Proffitt et al. at least suggests "calculating the number and/or percent of individual cells," as recited in claim 40. [emphasis added]

As demonstrated by the Examiner’s statement above, the claims and specifically the quoted claim limitations have not been considered in their entirety and have been misrepresented by the Examiner. The claim clearly recites “calculating a number and or percent of the **individual cells** that **internalized the labeled reporter molecule...**” not just “calculating a number and or percent of the individual cells” as represented by the Examiner’s responsive argument.

As argued by the Examiner, Proffitt teaches looking at the total fluorescence of the collection of cells in the well and then determining relative cell number. However, Proffitt does not teach “calculating a number and or percent of the **individual cells** that **internalized the labeled reporter molecule...**” As noted previously and above, the methods taught by Proffitt, which teaches looking at the **total fluorescence** of the collection of cells in the well, would result in an inability to distinguish between cells in which the receptor has internalized and cells in which the receptor is localized to the cell surface. In both circumstances the cell would emit the fluorescence and the methods of Proffitt would simply look at **total fluorescence** from the cells in the well. Thus, given the methods of Proffitt, it is not possible to calculate “**a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein**” as recited

in the instant claims. The Examiner has not addressed the quoted claim in its entirety including all limitations, but has stopped short and only addressed the claim limitation up to “a number and/or percent of the individual cells.” The Examiner has provided no evidence or support that Proffitt et al teaches calculating “a number and/or percent of the individual cells **that internalized the labeled cell surface receptor protein.**” The Examiner hasn’t even asserted that Proffitt et al teaches calculating “a number and/or percent of the individual cells **that internalized the labeled cell surface receptor protein.**” Thus, the Examiner has provided no evidence or support that Proffitt teaches the **entire claim limitation** for which Marks in view of Kallal is admitted to be deficient. The Patent Office has clearly stated on the record that “Marks in view of Kallal et al. does **not** teach calculating a number and or percent of the individual cells that internalized the at least first luminescently labeled reporter molecule.” Proffitt does not teach this **entire** claim limitation and thus does not cure the deficiencies of Marks in view of Kallal.

Thus, the combination of references cited by the Patent Office does not teach, suggest, or make obvious machine readable storage media for identifying internalized cell surface receptor proteins in multiple **individual cells** and calculating a number and/or percent of the **individual cells that internalized the labeled cell surface receptor protein** wherein the calculations provide a measure of internalization of the cell surface receptor protein in the **individual cells** and thus the Patent Office has not established a *prima facie* case of obviousness with respect to the invention of independent claim 40. Since the remaining claims all depend from claim 40, it is also clear that the Patent Office has not established a *prima facie* case of obviousness with respect to them.

Therefore, the Applicants respectfully request reconsideration and withdrawal of the rejection.

**B. The Office Erred in Rejecting Claim 43 under 35 U.S.C. § 103(a) as being obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al. as applied to claims 40-42 and further in view of Dunlay, et al.**

Claim 43 stands rejected as obvious over Marks, et al, in view of Kallal, et al in

further view of Proffitt, et al as applied to claims 40-42 and further in view of Dunlay, et al. For the reasons set forth in the Appeal Brief filed December 4, 2008 and the Reply Brief filed May 18, 2009 and for the following reasons, the Appellants respectfully traverse.

**i. The cited references alone or in combination do not teach or disclose all of the claim limitations**

In order to establish a *prima facie* case of obviousness the Patent office must establish that the prior art references alone or in combination must teach or suggest *all* the claim limitations. MPEP § 706.02(j).

As previously argued, Claim 43 is dependent on claim 40 and thus shares all of the claim limitations of claim 40. Marks et al in view of Kallal et al in further view of Proffitt do not teach, suggest or make obvious all of the claim limitations of claim 40 as outlined above in section A and previously in the Appeal Brief filed December 4, 2008 and the Appeal Brief filed May 18, 2009. The addition of Dunlay et al. does not cure the deficiencies of Marks et al, Kallal et al and Proffitt et al as applied to claim 40 and thus, the combination of all of the references does not teach suggest or make obvious the claim limitations of pending claim 40 or its dependent claim 43. Thus, it is clear that the Patent Office has not established a *prima facie* case of obviousness with respect to the invention of independent claim 40, nor the dependent claims, including claim 43. Therefore, the Applicants respectfully request reconsideration and withdrawal of the rejection.

**C. Conclusion**

In summary, the presently claimed methods cannot be rendered obvious by Marks, et al, in view of Kallal, et al in further view of Proffitt and further in view of Dunlay et al because Marks, et al alone or in combination with all of the further references does not teach all the elements of the presently pending claims. The combination of Mason et al. in view of Kallal et al and Proffitt et al provides no teaching or suggestion regarding methods or machine readable storage media for identifying internalized cell surface receptor proteins in multiple **individual cells** and calculating a number and/or percent of the **individual cells that internalized the labeled cell surface receptor protein** wherein the calculations provide a measure of **internalization** of the

cell surface receptor protein in the **individual cells**. Accordingly, the Applicants respectfully submit that this rejection is improper.

Date: November 11, 2009

Respectfully Submitted,

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